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PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 27 JUN 2005
WIPO PCT

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
002-ST-03-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT2004/000107	03.03.2004	17.04.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/205, A61P9/10

Applicant
SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.05.2004	27.06.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IT2004/000107

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-16 as originally filed

   Claims, Numbers

   1-17 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-9,13,14,16,17
	No:	Claims	1-6,10-12,15
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

5.1 The following documents (D) are referred to in this communication:

D1: ILICETO SABINO ET AL: "Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: The L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 26, no. 2, 1995, pages 380-387, XP002290008 ISSN: 0735-1097

D2: COLONNA PAOLO ET AL: "Myocardial infarction and left ventricular remodeling: Results of the CEDIM trial" AMERICAN HEART JOURNAL, vol. 139, no. 2 Part 3, February 2000 (2000-02), pages S124-S130, XP008033144 ISSN: 0002-8703

D3: MARTINA B ET AL: "Antiarrhythmic treatment with L-carnitine in acute myocardial infarction" SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT, vol. 122, no. 37, 1992, pages 1352-1355, XP008033145 ISSN: 0036-7672

D4: RIZZON P ET AL: "HIGH DOSES OF L CARNITINE IN ACUTE MYOCARDIAL INFARCTION METABOLIC AND ANTIARRHYTHMIC EFFECTS" EUROPEAN HEART JOURNAL, vol. 10, no. 6, 1989, pages 502-508, XP008033143 ISSN: 0195-668X

D5: SINGH R B ET AL: "A randomised, double-blind, placebo-controlled trial of L-carnitine in suspected acute myocardial infarction" POSTGRADUATE MEDICAL JOURNAL, vol. 72, no. 843, 1996, pages 45-50, XP008033142 ISSN: 0032-5473

5.2 In light of the documents cited in the international search report, claims 1 - 6, 10 - 12 and 15 do not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. do not appear to be novel and to involve an inventive step for the following reasons:

Document **D1** discloses a study conducted in patients with acute myocardial infarction who were admitted to hospital within 24 hours of onset of chest pain and treated with L-carnitine 9 g/day i.v. (5 days) and then 6 g/day orally (12 months) (page 381, left-hand column, "Methods"). Some of the patients were treated concomitantly with ACE inhibitors, beta-blockers or calcium antagonists (Table 2). The study shows that early and long-term administration of carnitine is effective in attenuating progressive left ventricular dilation (page 382, right-hand column, last paragraph). This

document is therefore considered to be relevant for novelty of claims 1 - 6, 10 - 12 and 15.

D2 also relates to a report about patients with acute myocardial infarction admitted to hospital within first 24 hours and treated with L-carnitine 9 g/day i.v. (5 days) followed by 6 g/day orally (12 months) (page S127, left-hand column). The paper suggests that early intervention with carnitine in the very acute phase of myocardial infarction may be a promising protective approach (page S129, left-hand column, 4th paragraph).

D3 shows an anti-arrythmic effect of L-carnitine observed in patients with acute myocardial infarction treated within 4 - 12 hours of onset of pain (page 1353, left-hand column, "Patienten und Methoden"; page 1354, right-hand column, "Diskussion").

D2 and D3 thus destroy novelty of the subject-matter of claims 1 - 5, 10 - 12 and 15.

D4 reports anti-arrythmic activity of L-carnitine (100 mg/kg i.v. every 12 hours) in patients with acute myocardial infarction admitted after 3 - 12 hours of onset of pain, wherein some of the patients were treated with a calcium antagonist at the same time (page 503, left-hand column, "Materials and Methods"; page 507, left-hand column, last paragraph; Table 6). D4 is therefore relevant for novelty of claims 1 - 6, 10 - 12 and 15.

D5 mentions that infarction enzyme markers and cardiac necrosis are reduced in patients with suspected acute myocardial infarction admitted to hospital within 10 hours of onset of pain and treated with 1.98 g L-carnitine p.o. during 28 days, eventually together with aspirin or beta-blockers (page 45, last paragraph; page 46, left-hand column, "Treatments"; page 46, left-hand column, "Study design"; page 48, right-hand column, 1st paragraph). D5 thus destroys novelty of claims 1 - 6, 10 - 12 and 15.

5.3 Dependent claims 7 - 9, 13, 14, 16 and 17 are formally novel. However, they do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(2) and (3) PCT).

Re Item VIII.

8.1 It is pointed out that second medical use claims 1 and 2 are not acceptable under Article 6 PCT. The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in form of a defined, real treatment of a

pathological condition or disease (**"reducing the number of deaths caused by acute myocardial infarction"** and **"improving the short- and long-term prognosis in the patients"**).

8.2 The terms **"few hours"** (claim 1), **"known drugs"** (claim 2), **"known mechanical and/or surgical techniques"** (claim 2) and **"any suitable dosage form"** (claim 15) are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

8.3 It is noted that the terms **"angiotensin converting enzyme inhibitors"** and **"ACE inhibitors"** relate to the same class of compounds. In order to meet the requirements of Article 6 PCT, it would be convenient to remove one of these terms.